MATTERS ARISING

Ankylosing spondylitis in west Africans—evidence for a non-HLA-B*27 protective effect

Dr Brown and his colleagues[1] are to be congratulated for performing a logistically formidable, but necessary, epidemiological study testing the currently in vogue hypothesis that the B*2703 subtype of HLA-B27 is not related to ankylosing spondylitis (AS). They conclude that the B*2705 subtype, as well as B*2703, possesses a lower risk for developing AS in a group of B27 positive west Africans, the Fula from Gambia, when compared with B27 positive white subjects invoking the potential protective role of an environmental factor(s). This conclusion is based on an assumed risk of developing AS in B27 positive persons of 11.1% for men and 1.5% for women.[2] No cases of AS were seen among 900 adult Fula men and 215 first degree relatives of 48 B27 positive Fula twin pairs. We would argue that the data warrant the more conservative conclusion implied in their discussion, namely, the risk for AS among B27 positive Fula subjects would need to be at least 2.7% in men and 1% in women to assign significance to the finding of no AS in this population.

The risk of developing AS in HLA-B27 positive subjects clearly varies among different ethnic groups, but it is now generally accepted that among white populations, the prevalence of AS is nearer 1–2% rather then 11.1%.[3 4] The Norwegian survey of 14 539 subjects[2] quoted by the authors is in fact based on a highly selected sample of only 375 people responding positively to a questionnaire for low back pain or stiffness who actually turned up for examination and had *x* rays of sacroiliac joints. You arrive at an entirely different conclusion if you apply the AS prevalence figures of 1.4% for B27 subjects from the Busselton population study[3] or 1.3% of Dutch B27 positive subjects.[4] The second study examined 2956 subjects older than 44 years who all had sacroiliac *x* rays and only three B27 positive subjects had AS according to the New York criteria leading to a prevalence of 0.1%. Recalculating the data of Brown *et al* according to these more generally accepted prevalence rates leads to the following conclusions. The probability of observing no cases of AS in 900 adult Fula men would be 46.9% (that is, p=0.47). The number of B*2703 persons expected to develop AS would be zero, as in fact observed in this population. Even assuming a risk of 2.7% for AS in B27 positive subjects, the likelihood that no cases of AS would be found in 900 adult Fula men is 23.2% (that is, p=0.232). Furthermore, we calculate that the prevalence of AS in the population of B27 positive adult Fula men would need to be at least 5.54% before the finding of zero observed cases of AS in 900 adult Fula men would be statistically significantly different.

We conclude that the issue of B*2703 and risk for AS remains an open question and in need of further more extensive population prevalence studies.

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Authors' reply

We would like to thank Dr Maksymowych for his interest in our study. We agree with his conclusion that our study shows that B27 is not associated with ankylosing spondylitis (AS) in the Gambia, as long as the risk of AS in B27 positive men is greater than 2.7% and women is greater than 1% (which we believe to be the case). We feel that most of his criticisms can be satisfactorily answered.

The risk of developing AS in B27 positive subjects is uncertain. The studies mentioned by Dr Maksymowych are among the lowest estimates that have been reported for white populations. Other studies have reported that as many as 20% of B27 positive subjects may develop the disease.[1] The survey by Gran *et al* is by far the largest reported[2]: 21 329 subjects were invited to participate in a study of cardiovascular disease, of whom 16 621 attended screening sessions. Of these, 14 539 (87%) completed questionnaires including questions about back problems; 2907 reported a history of pain or stiffness in the back—the remainder were asymptomatic. From this group a random sample of 806 were invited to attend for clinical screening, of which 449 did; 375 of these had sacroiliac radiography. Comparisons at each step demonstrated that selection bias was minimal. We believe therefore that not only is this study significantly larger than either of the studies mentioned by Dr Maksymowych, but is also reliable. It is also the only study of sufficient size to determine the risk for AS among men and women with B27 separately, which was a requirement for our analysis.

The risk for AS among B27 positive men is significantly greater than B27 positive women. In our study 1008 participants were male and 107 female. Therefore it was important to use sex-specific risk estimates, which Dr Maksymowych has not used in his calculations. Also, the study examined 215 relatives of 48 B27 positive subjects in addition to the 900 adult Fula men used in Dr Maksymowych's calculations. Analysing the total study population (n=1115), we showed that AS was not associated with B27 in the Gambia ($p<0.05$), assuming that the risk of AS was $\geq 1.85\%$ in B27 positive subjects, and that men were 2.7 times more likely to develop disease than women (both of these assumptions are conservative). Using a higher male:female ratio would allow us to exclude even lower degrees of association of B27 with AS.

Our study confirmed the previous finding that AS is extremely rare in west Africa—indeed no case has yet been reported from the Gambia.[3–5] This is despite the prevalence of B27 being as high as 7.8% in some ethnic groups.[6] The fact that 68% of B27 positive subjects in this area carry B*2705 indicates that it is not a difference in B27 subtypes that explains the rarity of the disease. Furthermore, two separate groups have now reported cases of AS in B*2703 subjects.[7 8]

It remains possible that B*2703 has a lower risk for AS than other disease associated subtypes. However AS is not associated with either B*2703 or B*2705 in the Gambia. Future comparisons of the strength of association of B27 subtypes with AS need to consider other environmental and genetic differences between the different populations studied.

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LETTERS

Serum uric acid in acute gout

The relation between gout and uric acid is such that in general clinical practice there is a tendency (diminishing) to misdiagnose gout in the presence of hyperuricaemia. Conversely the diagnosis of gout may be rejected when a normal serum uric acid (SUA) value is found. Given that a high proportion of estimations are made at the time of the acute episode a correct diagnosis may depend on a practitioner's knowledge of the fact that the SUA may be within the 'normal range' at this time. Most, if not all rheumatologists, are

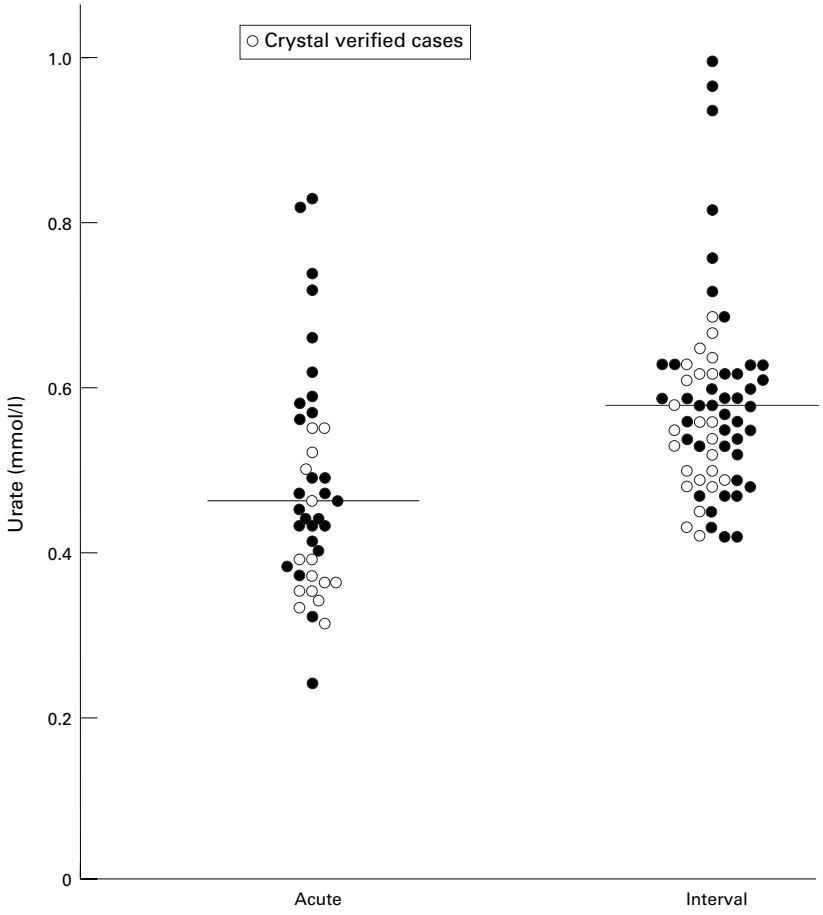

Figure 1 Urate values in acute and interval gout.

aware of this fact, although the emphasis in current general and rheumatological publications and text books is that this is an unusual occurrence.[1 2] We have conducted a prospective study to determine the frequency of normal SUA values in acute gout and also to compare acute and intercritical values.

Over a period of three years we observed 38 consecutive patients during 42 episodes of acute gout and who had the following characteristics: 34 men, four women, age 40–80 years mean 54: inpatients 16, domiciliary visits 9, Accident and Emergency 7, and clinic 10. Chronic diuretic drug use was implicated in eight and excessive alcohol in 10 patients. The diagnosis of acute gout was made on clinical grounds.[3] In 15 patients joint aspirate was positive for urate crystals. All had SUA measured during the acute attack. Patients taking allopurinol, uricosurics, aspirin (other than low dose) or azapropasone were excluded. Except for two patients from Accident and Emergency and four GP home visits all patients were seen by one of us during the acute bout.

Urate estimations after the episode were made either before commencement of allopurinol or within three months. Values before the episode (within six months) were available from the files of 20 patients. The upper limit of the normal range of SUA in our laboratory is 0.45 mmol/l in men and 0.38 in women. Figure 1 shows the SUA values for the acute and intercritical phases. The respective median values were 0.44 and 0.56 mmol/l for the whole group and 0.42 and 0.54 mmol/l for crystal verified cases ($p = 0.004$, Mann-Whitney). During the acute episode a normal SUA value was found in 43% as follows: 16 men and two women; 11 of 22 monoarticular, five of 12 polyarticular, and two of four chronic tophaceous gout; four of 10 excessive alcohol, three of eight diuretic use. In 14 men the value was below the saturation value of urate in serum (0.4 mmo/l). Five patients had one normal intercritical value and higher values at other times. In 30 of 42 (70%) the SUA during the acute episode was lower (that is, by <0.05 mmol/l), in seven it was unchanged, and in five it was higher than the intercritical value. These findings indicate that the SUA value usually falls during an acute episode and sometimes to within the normal range in all clinical varieties of gout and including those in whom excess alcohol and diuretic use is implicated. Snaith and Coomes[4] found a normal SUA in 17% of acute episodes of gout of unspecified type and Hadler *et al*[5] in 39% of polyarticular episodes. Both were retrospective case record studies, which may yield inaccurate prevalence data. In our prospective study a normal SUA occurred more often than is generally appreciated during the acute episode and occasionally at other times. We believe that highlighting the differences in the range of values in acute and intercritical gout in medical textbooks and laboratory reports will increase diagnostic accuracy and improve patient management.

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Giant cell arteritis of the leg in a patient with hepatitis C virus infection

The potential association of chronic hepatitis C virus (HCV) infection with a variety of dermatological features has been reported.[1] In particular, it has been observed that different types of cutaneous vasculitis may develop during the course of HCV infection,[1–5] such as mixed cryoglobulinaemia related leucocytoclastic vasculitis and polyarteritis nodosa.

We report a case of giant cell arteritis (GCA) involving the medium sized dermal arteries of the right leg, which appeared after a long history of HCV infection.

A 44 year old man with an eight year history of chronic hepatitis was admitted to the Rheumatology/Clinical Immunology Units of the University of Pisa in July 1995 because of erythematous cutaneous nodules on the legs. Chronic hepatitis had been suspected since 1987 because of raised, fluctuating values of hepatic enzymes. In 1993 the diagnosis was confirmed by liver biopsy. In June 1995 the presence of anti-HCV antibodies was demonstrated by an ELISA test. From the time of the histopathological assessment of chronic hepatitis to that of the appearence of the cutaneous nodules the patient was not receiving any medical treatment.

At the time of his stay in hospital the patient underwent a complete physical examination, which showed no abnormalities except for the cutaneous lesions. These were tender, red, and painful nodules situated on the medial side of the right leg, which appeared to be confluent in some areas.

Routine laboratory investigation showed only a moderate increase of the acute phase reactants (erythrocyte sedimentation rate 29 mm 1st h, C reactive protein 2.9 mg/dl, fibrinogen 600 mg/dl).

Antineutrophil cytoplasmatic antibodies (ANCA), antinuclear antibodies, immune complexes, and cryoglobulins were absent. Hepatitis B virus markers (antibodies to hepatitis B, anti-HBc, and anti-HBe, and the HBs and HBe antigens) were not detected in the serum, nor were the antibodies anti-HIV1 and -HIV2.

On the contrary, anti-HCV antibodies were found using a third generation ELISA test (Abbott HCV EIA 3.0, Abbott Diagnostics, Wiesbaden-Dielkenhein, Germany). A qualitative 'dot' assay (Abbott HCV MATRIX, Abbott Diagnostics, Wiesbaden-Dielkenhein, Germany) showed that these antibodies were directed to the HC-34 core and HC-29 NS3 recombinant proteins, while there was no serological reactivity against the c-100-3 NS4, HC-23 NS4 viral recombinant antigens.

The presence of viral RNA (indicative of active HCV replication) in the serum was demonstrated by a polymerase chain reaction